UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' BRIEF IN SUPPORT OF *DAUBERT* MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT FENGTIAN XUE, PH.D.

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PRELIMINARY STATEMENT

ZHP's expert in organic chemistry, Fengtian Xue, Ph.D., failed to apply a reliable methodology, and his opinions based on what he knows or would do rather than what ZHP could or should have done, do not "fit" the facts of the case. His opinions are untethered to the facts, and constitute net opinions. [redacted] This fragmented approach cannot fairly be termed a coherent methodology.

[redacted] But what he would have done is irrelevant to this case.

[redacted]

[redacted]

The Court should bar Dr. Xue's opinions in their entirety.

STATEMENT OF FACTS

Fengtian Xue, Ph.D is an organic chemist and professor at the University of Maryland, where he runs an experimental lab developing "pre-clinical … small molecule therapeutics for bacterial infections, alcohol use disorders, neurodegenerative diseases, and cancer." (https://faculty.rx.umaryland.edu/fxue/, Ex. 1; *see also* Xue R. 5, Ex. 2; Ex. B to Xue. R.; Xue. Dep. 68:12-69:18, Ex. 3).[1] [redacted] (Xue Dep. 69:17-18). [redacted] (*Id.* at 84:22-85:11). [redacted]

[1] Unless otherwise noted, all exhibits are from Adam M. Slater's certification in support of this motion.

[redacted]

(Xue R. 3). [redacted] (Xue Dep. 28:2-5, 30:11-13, 31:13-14, 46:8-10, 51:1-2, 52:2-3, 53:21-22, 65:8-14, 395:16-18).

THE *DAUBERT* STANDARD

The admissibility of expert testimony is determined pursuant to Federal Rule of Evidence 702. Preliminarily, "Rule 702 requires that the expert's testimony must assist the trier of fact." *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 742-43 (3d Cir. 1994). The Third Circuit has explained that "admissibility [consequently] depends in part on 'the proffered connection between the scientific research or test result to be presented and particular disputed factual issues in the case.'" *Id.* at 743 (quoting *U.S. v. Downing*, 753 F.2d 1224 (3d Cir. 1985)). Importantly, "scientific validity for one purpose is not necessarily scientific validity for other, unrelated purposes." *Id.* "Thus, even if an expert's proposed testimony constitutes scientific knowledge, his or her testimony will be excluded if it is not scientific knowledge **for purposes of the case**." *Id.* (emphasis added).

"As a gatekeeper, courts are supposed to ensure that the testimony given to the jury is reliable and will be **more informative than confusing**." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 800 (3d Cir. 2017) (emphasis added). Additionally, "[b]oth an expert's methodology and the application of that methodology must be reviewed for reliability." *Id.* at 791. The "specific way an expert conducts such an analysis must be reliable; '**all of the relevant evidence must be gathered**, and **the assessment or weighing of that evidence *must not be arbitrary***, but must itself be **based on methods of science.**'" *Id.* at 796. Here, the application of the proposed methodology is fatally flawed.

The party offering the proposed expert testimony bears the burden of establishing the admissibility of the testimony by a preponderance of the evidence. *Padillas v. Stork-Gamco, Inc.,* 186 F.3d 412, 417-18 (3d Cir. 1999). An "expert's opinions must be based on the methods and procedures of science, **rather than on subjective belief or unsupported speculation**." *Paoli*, 35 F.3d at 742 (emphasis added) (citations and internal quotations omitted). Thus, "the expert must have 'good grounds' for his or her belief." *Id.* (quoting *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 590 (1993)). These good grounds must support each step of the analysis and, "*any* step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible." *Id.* at 745. A court should also consider the methodology's error rate when assessing its reliability. *Id.* at 742 n.8. Judges within this Circuit also consider how and when the methodology is used outside of litigation. *Id.* at 742 (discussing reliability factors under *Daubert* and Third Circuit case law). [redacted]

Furthermore, "*Daubert*'s gatekeeping requirement .... make[s] certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom **the same level of intellectual rigor that characterizes the practice of an expert in the relevant field**.'" *Elcock v. Kmart Corp.*, 233 F.3d 734, 746 (3d Cir. 2000) (emphasis added) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)); *see also Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 594 (D.N.J. 2002*), aff'd,* 68 Fed. Appx. 356 (3d Cir. 2003). In addition, the following factors are relevant when determining reliability:

> (i) whether the expert's proposed testimony grows naturally and directly out of research the expert has conducted independent of the

> litigation (*see Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 43 F.3d 1311, 1317 (9th Cir. 1995)); (ii) whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion (*see General Elec. Co. v. Joiner,* 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)); (iii) **whether the expert has adequately accounted for alternative explanations** (*see Claar v. Burlington, N.R.R.,* 29 F.3d 499 (9th Cir. 1994)).

Magistrini, 180 F. Supp. 2d at 594–95 (emphasis added). To this end, the Third Circuit has affirmed the exclusion of expert testimony that "failed to consistently apply the scientific methods … articulate[d], … deviated from or downplayed certain well-established principles of [the] field, and … inconsistently applied methods and standards to the data so as to support [an] a priori opinion." *Zoloft*, 858 F.3d at 792. The same outcome is required on this record.

I.
DR. XUE'S OPINIONS
SHOULD BE PRECLUDED PURSUANT TO *DAUBERT*

A. Dr. Xue's Narrow Qualifications and Inadequate Methodology.

[redacted] (Xue Dep. 57:17-24, 63:3-5, 66:18-19 176:24-177:1).

[redacted] (*See, e.g.*, Xue Dep. 84:22-85:11; 259:20-23). This should factor into the Court's determination of reliability:

> One very significant fact to be considered is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying. That an expert testifies for money does not necessarily cast doubt on the reliability of his testimony, as few experts appear in court merely as an eleemosynary gesture. But in determining whether proposed expert testimony amounts to good science, we may not ignore the fact that a scientist's normal workplace is the lab or the field, not the courtroom or the lawyer's office.

Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1317 (9th Cir. 1995); s*ee also Elcock*, 233 F.3d at 747 (quoting *Paoli*, 35 F.3d at 742, n.8). Expert testimony prepared solely for purposes of litigation, as opposed to testimony flowing naturally from an expert's scientific research or technical work should be viewed with some caution. *Magistrini*, 180 F. Supp. 2d at 594.

[redacted]. *See Paoli*, 35 F.3d at 742-743 (holding an "expert's opinions must be based on the methods and procedures of science, **rather than on subjective belief or unsupported speculation**," and "admissibility depends in part on 'the proffered connection between the scientific research or test result to be presented and particular disputed factual issues in the case.'"); *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 241 (S.D.N.Y. 2018) (holding, **"[M]ethodology ... aimed at achieving one result ... is unreliable, and ... must be excluded"** (quoting *Faulkner v. Arista Records LLC*, 46 F. Supp. 3d 365, 381 (S.D.N.Y. 2014)).

In granting a motion to preclude an expert under *Daubert*, this Court has observed:

> [C]ourts also need not admit mere conclusions or opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered…. Mere assumptions, without causal evidence or methodological analysis may be inadmissible.... Conclusions based only on the expert's experience, and testimony founded on methods that are not generally accepted or lack testable hypotheses may also fail to surmount the *Daubert* standard.

Player v. Motiva Enterprises LLC, No. Civ. 02–3216(RBK), 2006 WL 166452, at *6-7 (D.N.J. Jan. 20, 2006) (citations omitted) (Ex. 9). In *Player*, this Court found the expert failed to satisfy the reliability requirement, as the expert failed to consider important facts without satisfactory explanation, among other things. *Id.* at *7. The Court held: "His method is untestable and arbitrary, without a generally accepted, established, or peer reviewed methodology, and his evaluation was conducted without any real standards." *Id.* at *8. [redacted]

(Xue Dep. 234:12-235:2). If he can't opine on that issue, there is no point to his testimony.

[redacted]

(Xue Dep. 176:18-22; 177:4-6). [redacted]

[redacted] (Xue Dep. 288:23-290:3). [redacted] (*Id.* at 214:17-20; 215:1-5; FDA, Guidance for Industry, *Genotoxic ad Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* (Dec. 2008), Ex. 10; HUAHIA-US00007898 (stating, [redacted]), Ex. 11; PRINSTON00080018 (same), Ex. 12). [redacted] (*Id.* at 162:5-8, 16-17). [redacted].[2] [redacted] (*Id.* at 156:3-158:5) [redacted]). [redacted]

[2] (Peng Dong 3/29/2021 Dep. Tr. 33:9-62:16, Ex. 13).

[redacted] (*Id.* at 296:13-21). [redacted].[3]

[redacted]

[redacted]

[redacted]

[3] In one narrow area where Dr. Xue did claim the ability to opine, he confirmed that [redacted] (*Id.* at 247:20-248:3). [redacted] (*Id.* at 248:5-11). This contradicts a central defense ZHP has attempted to maintain in this litigation.

[redacted]

(*Id.* at 191:18-192:19). [redacted] (*Id.* at 229:21-231:16). *Daubert* prohibits this type of subjective, conclusion-driven approach. *Mirena*, 341 F. Supp. 3d at 241 (S.D.N.Y. 2018) (holding, **"[M]ethodology ... aimed at achieving one result ... is unreliable, and ... must be excluded"** (quoting *Faulkner*, 46 F. Supp. 3d at 381)).

[redacted] World Health Organization's 2001 monograph on *N,N*-Dimethylformamide, [redacted] states that, "**DMF sold commercially contains trace amounts of … dimethylamine**." (Xue Dep. 124:13-126:21(quoting Long & Meek, *Concise International Chemical Assessment Document 31: N,N-Dimethylformamide* (WHO 2001), Ex. 14) (emphasis added)). This is important evidence showing that the DMA could, and likely would, be introduced to the manufacturing process without the need for the DMF to degrade and form the DMA during the manufacturing process. [redacted]

[redacted]

(*Id.* at 129:7-18). [redacted] Certificates of Analysis for DMF [redacted], easily found on the internet—stating the presence of DMA as an impurity of DMF. (*Id.* at 141:10-149:15 (discussing Shandong Hualu-Hengsheng Chem Co., *Certification of Analysis for N,H-Dimethylformamide*, Ex. 15)). [redacted] (*Id.* at 126:22-127:9). [redacted] (*Id.* at 127:13-17).

[redacted]

(*Id.* at 134:18-24). [redacted]

[redacted]

(*Id.* at 135:1-13).

[redacted]

(*Id.* at 136:13-17). [redacted]

(*Id.* at 136:20-23). [redacted]

[redacted] (*Id.* at 14-19). [redacted] (Xue R.; Xue Suppl. R., Ex. 23; Ex. A to Xue R.; Suppl. List, Ex. 16). [redacted] (Xue Dep. 138:20-23).

[redacted] (*Id.* at 136:22-23). [redacted] (*Id.* at 140:11-144:2 (discussing Ex. 4)). [redacted] the certificate of analysis showed the presence of dimethylamine as a documented impurity in the DMF as purchased. (*Id.* at 145:17-146:5, 149:7-15 (discussing Shandong Hualu-Hengsheng Chem Co., *Certification of Analysis forN,H-Dimethylformamide*, Ex. 15)). Importantly, the certificate of analysis is for batch number "20101026," indicating that the batch was produced in 2010. (Ex. 15). [redacted] (*Id.* at 153:20-154:8). [redacted]

[redacted] a November 25, 2012 certificate of analysis for triethylamine (the namesake of the TEA with sodium nitrite quenching process) found on the internet, that included a specification and positive test result for DEA as an impurity of that commercially purchased TEA. (*Id.* at 321:6-23 (discussing Ex. 17)). [redacted]

[redacted] (*Id.* at 323:4-13). [redacted] (*Id.* at 324:6-17). [redacted] yet another scientific article, this one from 1977, titled *Dimethylformamide: Purification Tests for Purity and Physical Properties*. (*Id.* at 164:14-24). The article states, "**Formic acid and dimethylamine are thus predominant impurities in DMF and determine the odor of the impure solvent…Owing to its various modes of degradation (hydrolysis, thermal and photochemical decomposition) the principle impurities found in DMF are: dimethylamine**" and then it lists some others. (*Id.* at 165:22-166:3, 184:1-7 (quoting Juillard, *Dimethylformamide: Purification, Tests For Purity And Physical Properties*, Int'l Union of Pure and Applied Chem (Pergamon Press 1977), Ex. 18). [redacted] (*Id.* at 184:8-185:8). [redacted]

[redacted]

(*Id.* at 188:21-189:19). [redacted] (*Id.* 189:22-191:2).

In order for Dr. Xue's opinions to be admissible, "the process or technique used in formulating the opinion [must be] ... reliable," and the principles and methods employed by the expert must be applied, "reliably to the facts of the case." *Pineda v. Ford Motor Co.*, 520 F.3d 237, 243 n.10, 247 (3d Cir. 2008) (citing Fed. R. Evid. 702; *Paoli,* 35 F.3d at 742). "'[A]n expert may not 'pick and choose' from the scientific landscape and present the Court with what he believes the final picture looks like.' **Where an expert ignores evidence that is highly relevant to his [or her] conclusion, contrary to his [or her] own stated methodology, exclusion of the expert's testimony is warranted.**" *Mirena II*, 341 F. Supp. 3d at 242 (quoting *In re Rezulin Prod. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004)).

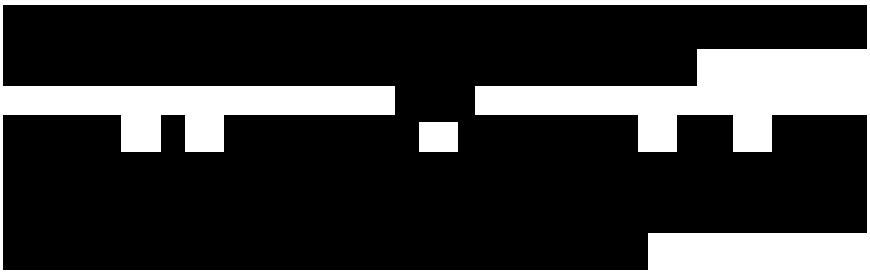
Dr. Xue's opinions are inconsistent with the scientific literature and other documentation showing that ZHP's processes could create nitrosamines, all of which was published before the development of those manufacturing processes. Unable to dispute the existence of this literature and other documentation, [redacted]

[redacted]

[redacted] This subjective "see no evil" approach is not a reliable methodology. *See id.* at 242 (quoting *Rezulin*, 309 F. Supp. 2d at 563); *see also In re Zoloft Products Liability Litigation,* 26 F. Supp. 3d 449, 460-61 (E.D. Pa. 2014) (citing *In re Rezulin Products Liability Litigation,* 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005) **("[I]f the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable.**")).

Dr. Xue's approach had even more holes. [redacted] (E.g. PRINSTON00075797, Ex. 4). [redacted] (Xue Dep. 57:17-24). The attempt to wall Dr. Xue off from damaging evidence is obvious, and only weakens his standing as an expert here. [redacted]

(*Id.* at 197:19-200:9 (quoting Ex. 4)).



(*Id.* at 202:4-205:6 (quoting Ex. 4)).

(Xue R. 3). (*See, e.g.*, PRINSTON00075809-10, Ex. 4; PRINSTON00075876, Ex. 4; PRINSTON0076108, Ex. 5).

(Xue Dep. 156:3-158:5). Moreover, the expert Dr. Xue's counterpart, Dr. Hecht, DID explicitly reference this issue in his reports. For example, in discussing the deviation investigation reports:

"The documents from ZHP clearly demonstrate how the formation of NDMA could have been avoided….the dimethyl formamide may have contained trace amounts of dimethylamine or the dimethylamine was formed during the process…The contamination of dimethyl formamide with dimethylamine or the formation of dimethylamine during the process was foreseeable, and should have been evaluated." and "Lower amounts of NDEA were also formed due to trace amounts of diethylamine present in the trimethylamine used as a catalyst in the tetrazole formation step, and/or by direct nitrosation of trimethylamine. All of this was foreseeable, and if considered and tested for, the NDEA contamination would have been detected." (July 6, 2021 Report of Ste hen Hecht, Ph.D., at 20-21, Ex. 24). [redacted] (Min Li 4/20/21 Dep. Tr., 77:8-80:16). [redacted] (Jun Du 5/28/21 Dep. Tr., 232:18-234:6, Ex. 25; cited in October 31, 2022 Supplemental Report of Dr. Hecht at 3, Ex. 26). [redacted] (Xue Dep. 131:7-14, 208:24-209:5). H [redacted] (Xue R.; Xue Dep. 209:13-210:4). [redacted] (Xue R.; Xue Dep. 236:22-237:4). [redacted]

[redacted],[4] [redacted]

[redacted]:

[redacted]

(Xue Dep. 236:11-239:18 (discussing PRINSTON0076108, Ex. 5 (citing Sun, Liu and Zhong, *Theoretical Investigation of N-Nitrosodimethylamine Formation from Nitrosation of Trimethylamine*, J. Phys. Chem. A. 114, 455-465 (2010), Ex. 7)); *see also id.* at 245:3-17). [redacted]

[redacted]

[redacted]

(*Id.* at 242:10-243:10). [redacted]

[redacted] (*Id.* at 244:23-245:23). [redacted]

[redacted]

[4] (PRINSTON00158436-37, Ex. 6).

[redacted]

(*Id.* at 282:20-286:7).[5] [redacted].[6]

[redacted] *Zoloft*, 858 F.3d at 769, 792 ("**all of the relevant evidence must be gathered**, and **the assessment or weighing of that evidence *must not be arbitrary***, but must itself be **based on methods of science.**"); *Paoli*, 35 F.3d at 742.

B. Dr. Xue impermissibly [redacted].

[redacted]

[5] [redacted] (*Id.* at 290:17-291:3).

[6] [redacted] another relevant article published in 1979 also described the nitrosation of tertiary amines such as TEA. (*Id.* at 257:1-258:24, 268:24-270:18 (discussing Gowenlock, Hutchinson, Little, Pfab, *Nitrosative dealkylation of some symmetrical tertiary amines,* J. Chem. Soc., Perkin Trans. 2, 1110-1114 (1979), Ex. 8)). [redacted]

[redacted]. (Ex. 21). [redacted] Such baseless ipse dixit is not helpful to a jury and is impermissible under *Daubert*. *See, e.g.*, *Player*, 2006 WL 166452, at *6-7.

The email was sent by ZHP drug impurity researcher Jinsheng Lin, Ph.D. to numerous high-level ZHP employees and matter-of-factly and CORRECTLY stated in part that ZHP's valsartan contained NDMA, and that it formed due to the sodium nitrite quenching. As testified to by Dr. Lin's boss, Min Li during his 30(b)(6) deposition, the email stated:

> Through the secondary mass spectrometry analysis, it can be inferred that the extra NO substituent is in the cyclic compound fragment, and it is very likely that it is an N-NO compound; **it is similar to the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite, and its structure is very toxic.**
>
> * * *
>
> **If it is confirmed as the above speculated structure, then its toxicity will be very strong, and there will be an extremely high GMP risk**. **This is a common problem in the production and synthesis of sartan APIs**. **It is recommended** to improve other quenching processes (such as NaClO) along with **the optimization of the valsartan sodium azide quenching process.**
>
> * * *
>
> I've also attached a patent of a 2013 sodium azide NaClO quenching method by Zhejiang Second Pharma Co., Limited. They proposed that the use of NaNO2 quenching will result in the formation of N-NO impurities. At the same time, they used ZHP's crude Valsartan in their LC-MS test and detected this impurity. **This indicates that other companies have paid attention to the quality problem very early on. So leaders please pay attention to this issue.**

(Min Li 4/20/2021 Dep. 87:19-88:7, 88:13-89:18, Ex. 19 (quoting Ex. 20) (emphases added)). [redacted] (Xue Dep. 340:14-341:5). [redacted]

[redacted]

(*Id.* at 336:22-338:15). [redacted] (*Id.* at 343:19-344:2, 346:7-16 (quoting Ex. 21)). However, [redacted] ZHP's Court-submitted, "true and correct" translation matches the other translations in the record, referring to "the N-nitrosodimethylamine group produced by the quenching of valsartan with sodium nitrite." (*Id.* at 347:16-384:12 (quoting Ex. 21)).

[redacted]

[redacted] (*Id.* at 20:15-24:3). [redacted] (*Id.* at 20:21-24). [redacted] (*Id.* at 21:8-23). [redacted] (*Id.*). [redacted] This was purely litigation driven and intended to escape the record compiled in discovery, nothing more.

C. Dr. Xue Provided a Pre-Determined Conclusion.

Dr. Xue also failed to contend with contrary facts in reaching his pre-determined conclusion—matching ZHP's talking points through years of discovery. [redacted] (Xue R. 56-57). [redacted]

[redacted]

valsartan, **do you agree it's something you should take into**

[redacted]

[redacted]

(Xue Dep. 394:20-397:18 (discussing Min Li 4/22/2021 Dep. 528:14-20, 529:17-530:4, Ex. 22)). This rambling testimony is emblematic of responses provided throughout the deposition. The failure to consider and integrate damaging evidence, or to explain his approach to that evidence in a cogent way, including something as starkly relevant as ZHP's own admissions as to central facts in this case, renders the testimony unhelpful to a jury. *Zoloft*, 858 F.3d at 800 ("As a gatekeeper, courts are supposed to ensure that the testimony given to the jury is reliable and will be **more informative than confusing**."). The failure to deal with contrary evidence is too pervasive here to be permitted. *Player v. Motiva Enterprises LLC*, No. Civ. 02–3216(RBK), 2006 WL 166452, at *6-7 (D.N.J. Jan. 20, 2006).

CONCLUSION

For the foregoing reasons, Dr. Xue failed to adopt or apply a reliable methodology, and he should therefore be precluded from offering his proffered opinions.

Respectfully,

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Dated: March 13, 2023